ELECTRONIC LETTER

Hypogonadotrophic hypogonadism, short stature, cerebellar ataxia, rod-cone retinal dystrophy, and hypersegmented neutrophils: a novel disorder or a new variant of Boucher-Neuhauser syndrome?

A-K Jbour, A F Mubaidin, M Till, H El-Shanti, A Hadidi, K M Ajlouni

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A number of syndromes have been described in which hypogonadotrophic hypogonadism is associated with multiple somatic and neurological anomalies such as tall stature, anosmia, ataxia, mental retardation, and choroidal dystrophy.[1–7] The large number of syndromes indicates the considerable clinical heterogeneity associated with hypogonadotrophic hypogonadism. In this report, we describe an unusual constellation of neuroendocrinological findings in an Arab family with three affected sibs. A major finding is hypogonadotrophic hypogonadism associated with short stature owing to gonadotrophic and somatotrophic cellular dysfunction in the anterior pituitary. Although, we discuss several possible modes of inheritance, we speculate that the mode of inheritance of this disorder in this family is autosomal recessive.

Key points

- Several syndromes with hypogonadotrophic hypogonadism and ataxia have been published. We report three sibs with progressive cerebellar ataxia with cerebellar atrophy, progressive decline in intellect, partial anterior pituitary dysfunction presenting as short stature owing to growth hormone deficiency and hypogonadism, progressive rod-cone dystrophy with bilateral ptosis, and hypersegmented neutrophils.
- We conclude that our patients may present a new variant of the Boucher-Neuhauser syndrome, because of some similarities, or may be a novel disorder. The mode of inheritance of this condition is most probably autosomal recessive.

PATIENTS, MATERIALS, AND METHODS

The family was ascertained through the proband VI.5 (fig 1). All three seemingly affected family members had a detailed evaluation by an endocrinologist, a neurologist, a clinical geneticist, and an ophthalmologist. Three of the four older sibs were examined by the same team and were reported to be normal. The three affected subjects also had electrocardiograms, echocardiograms, brain and pituitary MRI, electromyography, nerve conduction studies, electroretinograms, and electro-oculograms.

Patient 1 (VI.5)

This male patient is currently 21 years old. He was the product of a 35 week gestation born by normal spontaneous vaginal delivery. At birth, he developed respiratory distress requiring neonatal intensive care for about 6 weeks. He achieved the early milestones of development on time but there is no available record for his growth pattern during the early years.

The onset of symptoms was gradual with a slowly progressive ataxic gait around the age of 6 years, which was associated with a progressive decline in his scholastic performance. He presented to us at the age of 20 years, and his height was 1.45 m (<5th centile), weight was 39 kg (<5th centile), and head circumference was 50.5 cm (>2 SD below the mean). He had mild non-progressive bilateral ptosis, and the genital examination showed an infantile penis, small testes, and sparse pubic hair. He had no dysmorphic features or obvious anomalies in the skeletal or cardiovascular systems. He showed evidence of mild impairment of cognitive function (Weschler intelligence scale: verbal IQ 69, performance IQ 47, and full IQ 54). Scanning, dysarthric speech, and multidirectional jerky nystagmus were present. While the saccadic eye movement was abnormal with bilateral hypometric saccades, pursuit eye movement was normal and he had no visual complaints.

The neurological evaluation showed normal muscle bulk, without wasting or fasciculations, normal strength throughout, and generalised hypotonia. The deep tendon reflexes were +2 and symmetrical, with a flexor plantar reflex. There were no sensory abnormalities on deep or superficial evaluation. Dysmetria, past pointing, dysdiodochokinesia, and intentional tremors were present bilaterally and symmetrically. He had a wide based gait, swaying in all directions, and was unable to tandem walk. Electromyography and motor and sensory nerve conduction studies were normal, including studies of the late responses.

On ophthalmological examination, colour vision was normal and the pupillary reactions, anterior segment, and intraocular pressure were all normal. He had astigmatism and the best corrected vision was 6/24 in both eyes. Indirect fundoscopic examination by a superficial lens showed posterior pole atrophic pigmentary retinopathy, while the optic nerves looked healthy. Fluoroscein angiography showed "window defect" atrophic retinal and retinal pigment epithelium in the posterior pole. The electroretinogram (photopic and scotopic) showed a rod-cone system dysfunction, more in the rods. The electro-oculogram was normal. The visual field could not be assessed.

MRI of the brain showed cerebellar atrophy, normal vermis, and dilatation of the sulci and subarachnoid space (fig 2). The left wrist, elbow, and pelvic *x* ray showed normal bone texture, but the radiological bone age was delayed (15-16 years).

Routine blood and urine testing, serum immunoglobulins, alpha-fetoprotein, ECG, echocardiogram, and chest radiographs were all normal. Despite a normal neutrophil count, 24% of the neutrophils contained five or more nuclear segments. Antinuclear antibodies (ANA), serum B12, serum folate, and serum ferritin were normal. Anti-parietal cell antibodies and the nitroblue-tetrazolium (NBT) test were normal. The karyotype, at a resolution of 550 bands, was of a normal

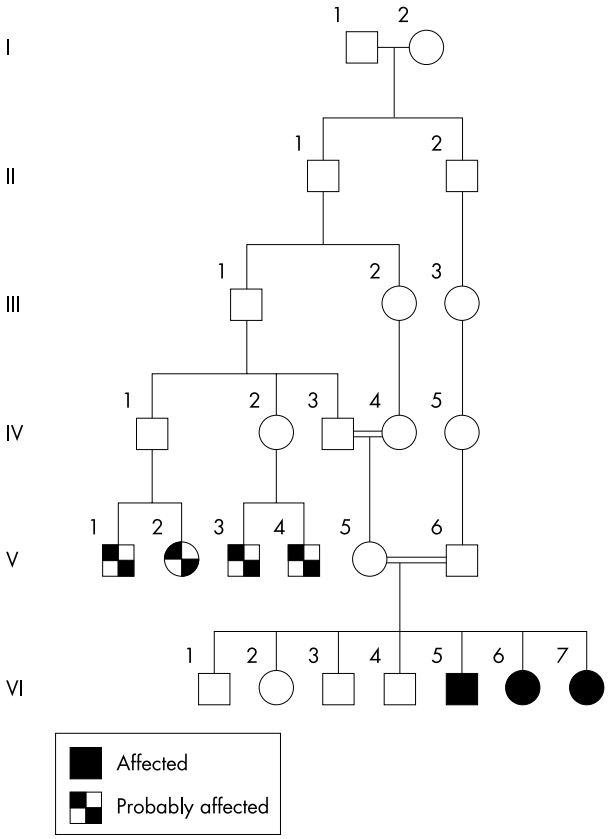

Figure 1 The family pedigree showing the three affected sibs (VI.5, VI.6, VI.7) and indicating the consanguinity. There are four possibly affected relatives (V.1, V.2, V.3, V.4).

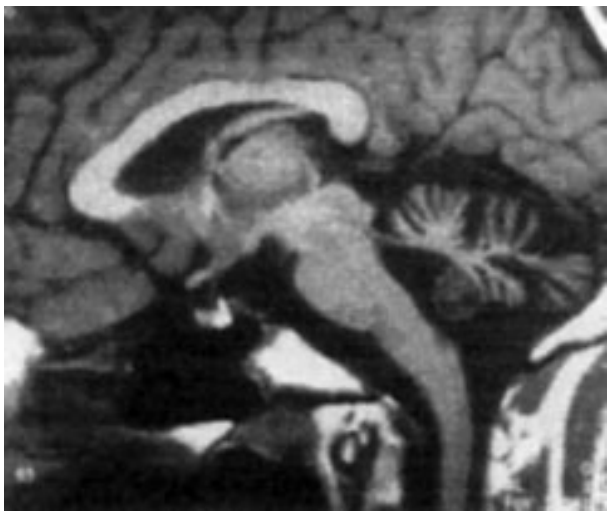

Figure 2 Sagittal T1 weighted MRI image of the brain, showing generalised cerebellar atrophy.

male (46,XY) without noticeable structural abnormalities. There was no evidence of fat malabsorption by Sudan III staining of stools. The audiogram showed normal hearing. LHRH stimulation test showed low baseline LH and FSH without response. There was no significant change in LH and FSH levels after priming with 10 IM injections of 100 μg of LHRH given 12 hourly, suggesting a primary pituitary defect. All LH and FSH readings were less than 2 IU/l. Growth hormone stimulation test showed no response to either L-dopa (before and after priming with 100 mg depot testosterone) or insulin induced hypoglycaemia. Serum TSH, prolactin, and cortisol levels were normal both at baseline and after stimulation with TRH and insulin hypoglycaemia test, respectively. There was a low serum testosterone level (1.2 ng/ml, reference range 3-10 ng/ml).

Patient 2 (VI.6)

This female patient is currently 17 years old, with a normal birth history and normal early childhood development. The onset of ataxia was similar to her older brother. At the age of 16 years her height was 138 cm (<5th centile), weight was 36 kg (<5th centile), and head circumference was 50 cm (>2 SD below the mean). The breast buds and pubic hair were prepubertal without menarche. The neurological evaluation showed findings exactly similar to her older brother. The visual acuity was 6/9 in the right eye and 6/12 in the left eye. The remainder of the ophthalmological evaluation yielded results similar to her older brother. The MRI of the brain showed generalised atrophy of the cerebellar hemisphere with dilatation of the subarachnoid space. The radiological bone age was delayed (13 years). Abdominal ultrasound scanning showed a small hypoplastic uterus, but the ovaries could not be identified. Nineteen percent of her peripheral blood neutrophils were hypersegmented. The karyotype, at a resolution of 550 bands, was of a normal female (46,XX) without noticeable structural abnormalities. The LHRH stimulation test showed low baseline LH and FSH without response. There was no significant change in LH and FSH levels after priming with 10 IM injections of 100 μg of LHRH, given 12 hourly. All LH and FSH readings were less than 2 IU/l. The oestrogen level was also low before and after stimulation. The remainder of the endocrinological laboratory workup was normal, as reported in the older brother.

Patient 3 (VI.7)

This female patient is currently 14 years old, with a normal birth history and normal early childhood development. The onset of ataxia was similar to her older sibs. At the age of 13 years her height was 137 cm (<5th centile), weight was 36 kg (<5th centile), and the head circumference was 49.5 cm (>2 SD below the mean). The breast buds and pubic hair were prepubertal without menarche. The neurological evaluation showed findings exactly similar to her older sibs. Visual acuity was 6/18 in both eyes. The remainder of the ophthalmological evaluation yielded results similar to her older sibs. The MRI of the brain showed generalised atrophy of the cerebellar hemisphere. Twenty-five percent of her peripheral blood neutrophils were hypersegmented. The karyotype, at a resolution of 550 bands, was of a normal female (46,XX) without noticeable structural abnormalities. The LHRH stimulation test showed low baseline LH and FSH without response. There was no significant change in LH or FSH levels after the previously mentioned priming method. All LH and FSH readings were less than 2 IU/l. The oestrogen level was also low.

DISCUSSION

The main features of the three sibs described in this report are progressive cerebellar ataxia with cerebellar atrophy, progressive decline in intellect, partial anterior pituitary dysfunction presenting as short stature owing to growth hormone deficiency and hypogonadotrophic hypogonadism, progressive rod-cone dystrophy with bilateral ptosis, and hypersegmented neutrophils. The decline in intellect was shown by progressive decrease in their scholastic achievement noticeable before any visual complaints. Neutrophil hypersegmentation has been defined as the presence of at least 5% of neutrophils with five or more lobes.[13]

The association of cerebellar ataxia and hypogonadotrophic hypogonadism has been reported previously (OMIM 212840).[1–3] In two reports the hypogonadotrophic hypogonadism was the result of deficiency of the hypothalamic LHRH.[1 2]

In the third report, the cause was concluded to be because of primary deficiency in the anterior pituitary.[3] In these three reports there was no mention of retinal changes.[1–3] The absence of retinal findings, the later onset of ataxia, and the hypothalamic origin of hypogonadism in two out of the three reports are the differentiating features from our report. The Boucher-Neuhauser syndrome (OMIM 215470) is composed of spinocerebellar ataxia, hypogonadotrophic hypogonadism, and chorioretinal dystrophy.[4–12] There are several distinguishing features between our reported patients and previous reports of Boucher-Neuhauser syndrome. First, the ataxia is spinocerebellar in the Boucher-Neuhauser syndrome, though the spinal component was not always mentioned,[10] whereas in our patients the ataxia was purely cerebellar. Secondly, the onset of ataxia is later in Boucher-Neuhauser syndrome, although in a few patients the onset was early in the second decade (before 15 years).[10] In our patients the onset of ataxia was in the first decade (6 years). Thirdly, in Boucher-Neuhauser syndrome the choroid is always involved, but the eye findings are quite variable.[10] In our patients, the choroid was clearly not involved. Lastly, our patients had hypersegmentation of the neutrophilic nuclei, a feature not mentioned in Boucher-Neuhauser syndrome. It is difficult to know if this feature was looked for in reported patients with Boucher-Neuhauser syndrome or not. The subtlety of the differences and the overall similarity of the clinical picture of our patients to the reported patients with Boucher-Neuhauser syndrome suggest that this is a new variant of that phenotypic spectrum. However, these differences may be real, thus suggesting a novel disorder.

The most likely mode of inheritance of the disorder described in this family is autosomal recessive because of the recurrence in the same sibship, the normal parents, and the consanguinity. There is mention of relatives with a similar phenotype but these subjects were not available for examination and the description relayed to us was not very clear because of social reasons. This mode of inheritance is in keeping with the Boucher-Neuhauser syndrome. It is equally plausible, despite the normal karyotype, that a chromosomal microdeletion is the cause of the disorder in this family. Cryptic chromosomal rearrangements and small deletions might not be elucidated at this level of resolution. We speculate that the gene involved in this previously undescribed syndrome plays a role in the development of the anterior pituitary, cerebellum, and retinal cells, as well as maintaining their integrity. It probably plays a role in neutrophilic morphology or its release from the bone marrow. The elucidation of the gene mutated in this disorder may shed some light on the normal developmental process of the tissues involved.

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Authors' affiliations
A-K Jbour, H El-Shanti, K M Ajlouni, National Centre for Diabetes, Endocrinology and Genetics, Amman, Jordan
A F Mubaidin, Department of Internal Medicine, King Hussein Medical Centre, Amman, Jordan
M Till, Department of Ophthalmology, Jordan University Hospital, Amman, Jordan
H El-Shanti, Department of Paediatrics, Jordan University of Science and Technology, Irbid, Jordan
A Hadidi, Department of Radiology, Jordan University Hospital, Amman, Jordan

Correspondence to: Dr H El-Shanti, PO Box 2983, Amman 11821, Jordan; hatem@just.edu.jo

REFERENCES

1 **Volpe R**, Metzler WS, Johnston MW. Familial hypogonadotrophic eunuchoidism with cerebellar ataxia. *J Clin Endocrinol* 1963;**23**:107-15.
2 **Berciano J**, Amado JA, Freijanes J, Rebollo M, Vaquero A. Familial cerebellar ataxia and hypogonadotropic hypogonadism: evidence for hypothalamic LHRH deficiency. *J Neurol Neurosurg Psychiatry* 1982;**45**:747-51.
3 **Abs R**, Van Vleymen E, Parizel PM, Van Acker K, Martin M, Martin JJ. Congenital cerebellar hypoplasia and hypogonadotropic hypogonadism. *J Neurol Sci* 1990;**98**:259-65.
4 **Boucher BJ**, Gibberd FB. Familial ataxia, hypogonadism and retinal degeneration. *Acta Neurol Scand* 1969;**45**:507-10.
5 **Neuhauser G**, Opitz JM. Autosomal recessive syndrome of cerebellar ataxia and hypogonadotropic hypogonadism. *Clin Genet* 1975;**7**:426-34.
6 **Limber ER**, Bresnick GH, Lebovitz RM, Appen RE, Gilbert-Barness EF, Pauli RM. Spinocerebellar ataxia, hypogonadotropic hypogonadism, and choroidal dystrophy (Boucher-Neuhauser syndrome). *Am J Med Genet* 1989;**33**:409-14.
7 **Baroncini A**, Franco N, Forabosco A. A new family with chorioretinal dystrophy, spinocerebellar ataxia and hypogonadotropic hypogonadism (Boucher-Neuhauser syndrome). *Clin Genet* 1991;**39**:274-7.
8 **Tojo K**, Ichinose M, Nakayama M, Yamamoto H, Hasegawa T, Kawaguchi Y, Sealfon SC, Sakai O. A new family of Boucher-Neuhauser syndrome: coexistence of Holmes type cerebellar atrophy, hypogonadotropic hypogonadism and retinochoroidal degeneration: case reports and review of literature. *Endocr J* 1995;**42**:367-6.
9 **Salvador F**, Garcia-Arumi J, Corcostegui B, Minoves T, Tarrus F. Ophthalmologic findings in a patient with cerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy. *Am J Ophthalmol* 1995;**120**:241-4.
10 **Rump R**, Hamel BC, Pinckers AJ, van Dop PA. Two sibs with chorioretinal dystrophy, hypogonadotrophic hypogonadism, and cerebellar ataxia: Boucher-Neuhauser syndrome. *J Med Genet* 1997;**34**:767-71.
11 **Erdem E**, Kiratli H, Erbas T, Varli K, Eldem B, Akalin S, Tan E, Topaloglu H, Gedikoglu G. Cerebellar ataxia associated with hypogonadotropic hypogonadism and chorioretinopathy: a poorly recognized association. *Clin Neurol Neurosurg* 1994;**96**:86-91.
12 **Fok AC**, Wong MC, Cheah JS. Syndrome of cerebellar ataxia and hypogonadotrophic hypogonadism: evidence for pituitary gonadotrophin deficiency. *J Neurol Neurosurg Psychiatry* 1989;**52**:407-9.
13 **Westerman DA**, Evans D, Metz J. Neutrophil hypersegmentation in iron deficiency anemia: a case-control study. *Br J Haematol* 1999;**107**:512-15